Productivity Savings from Colorectal Cancer Prevention and Control Strategies

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Appendix A

The MISCAN-Colon microsimulation model and productivity cost estimation

OUTLINE

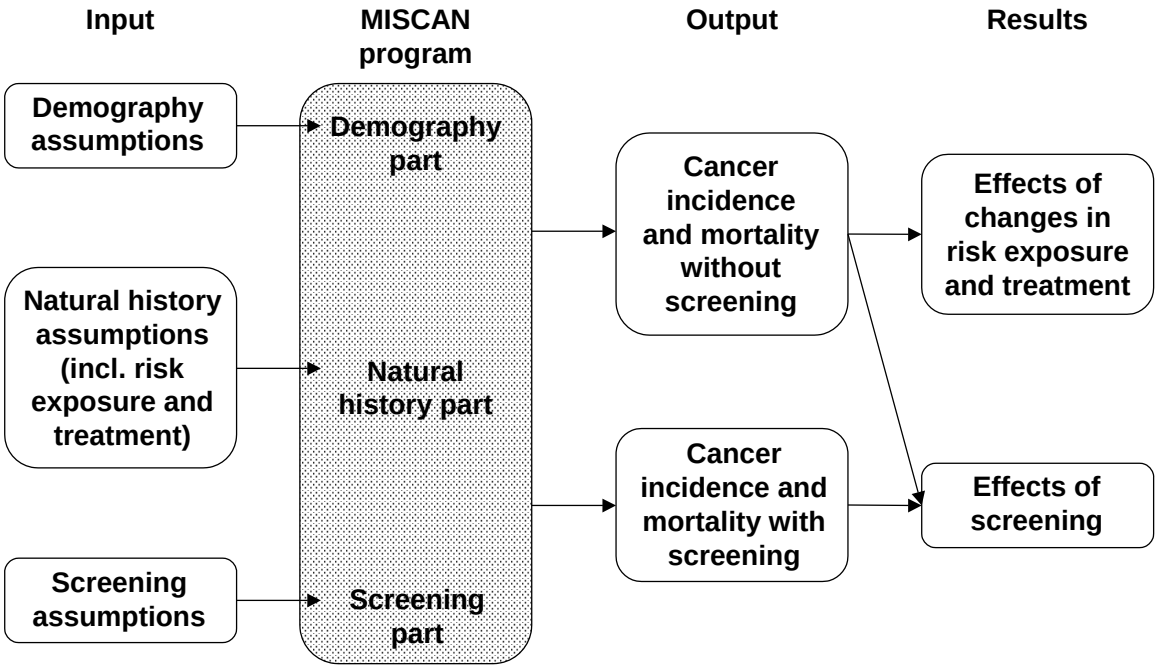
MODEL OVERVIEW

The MISCAN-Colon model is a semi-Markov microsimulation model. The population is simulated individual by individual, and each person can evolve through discrete disease states. However, instead of modeling yearly transitions with associated transition probabilities, the MISCAN-Colon model generates durations in states. The advantage of the MISCAN approach is that durations in a certain state need not necessarily be a discrete value but, rather, can be continuous. MISCAN uses the Monte Carlo method to simulate all events in the program. Possible events are the birth and death of a person, adenoma incidence, and transitions from one state of disease to another.

The basic structure of MISCAN-Colon is illustrated in Appendix Figure 1, which clearly demonstrates that MISCAN-Colon consists of three parts:

- demography part
- natural history part
- screening part

These parts are not physically separated in the program, but it is useful to consider them separately.



Appendix Figure 1: Structure of MISCAN-Colon miscrosimulation model.

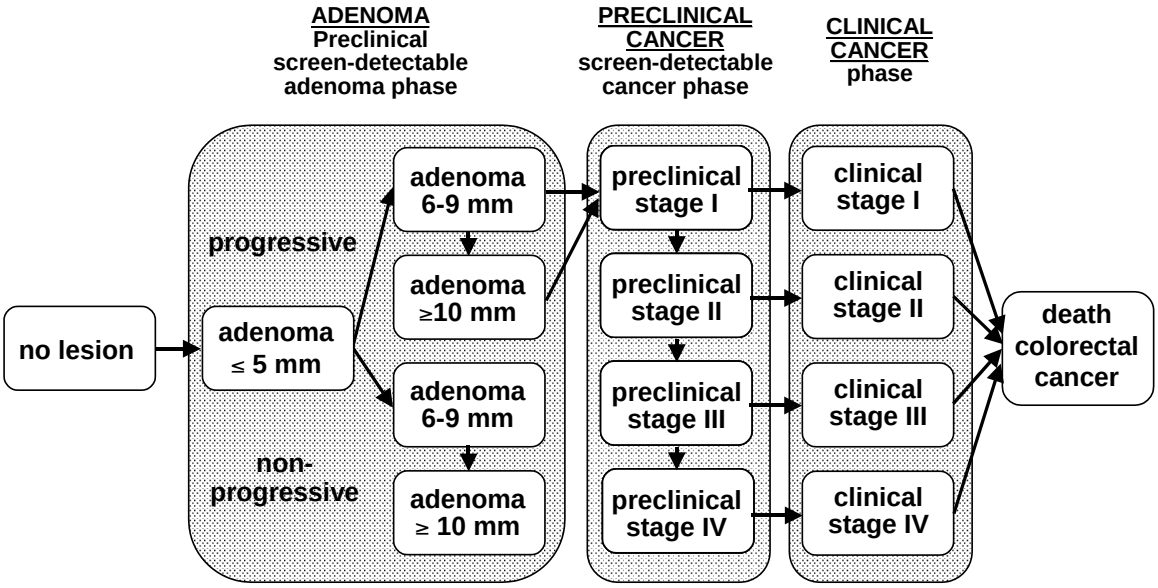
DEMOGRAPHY PART

The demography part of the model simulates individual life histories without colorectal cancer to

form a population. For each person, a date of birth and a date of death from causes other than colorectal cancer are simulated. The distributions of births and deaths can be adjusted to represent the population simulated. For example, a population of Caucasian females will have older ages at death than a population of African American males.

NATURAL HISTORY PART

The Natural History part of MISCAN-Colon simulates the development of colorectal cancer in the population. We assume that all colorectal cancers develop according to the adenoma–carcinoma sequence as described by Morson (1) and Vogelstein et al. (2) (Appendix Figure 2). For each individual in the simulated population, a personal risk index is generated. Subsequently, adenomas are generated in the population according to this personal risk index and an age-specific incidence rate of adenomas. This risk index results in no adenomas for most persons and one or more adenomas for the others. The distribution of adenomas over the colorectum is simulated according to the observed distribution of colorectal cancer incidence. Each of the adenomas can independently develop into colorectal cancer. Adenomas can progress in size from small (1–5 mm) to medium (6–9 mm) to large (≥10 mm). Most adenomas will never develop into cancer (non-progressive adenomas); the ones that do (progressive adenomas) may eventually become malignant, transforming to a stage I cancer. The cancer may then progress from stage I to stage IV. In every stage, there is a chance that the cancer will be diagnosed because of symptoms. The survival after clinical diagnosis depends on the stage of the cancer.



Appendix Figure 2: Adenoma and cancer stages in the MISCAN-Colon model. Cancer stages correspond to the American Joint Committee on Cancer / International Union Against Cancer staging system for colorectal cancer (3). Adenomas are categorized by size. The size-specific prevalence of adenomas as well as the proportion of adenomas that ever develop into cancer is dependent on age of adenoma onset.

The impact of changes in risk factors and treatment is incorporated in the natural history part. Risk factors, such as obesity, smoking and red meat consumption, are assumed to increase the risk of colorectal cancer by increasing the age-specific onset of adenomas. This way more adenomas are present to develop into colorectal cancer, and thus more colorectal cancers will arise. Protective factors, such as physical activity, fruit and vegetable consumption and use of folate, aspirin or hormone replacement therapy, are assumed to decrease the risk of colorectal cancer by decreasing the onset of adenomas. Fewer adenomas mean that fewer adenomas can develop into colorectal cancer and thus reducing incidence. The relative risk associated with each risk and protective factor determines the level with which the onset of adenomas is increased or decreased.

Changes in chemotherapy are modeled by improvements in stage-specific survival after diagnosis. We used survival estimates from SEER for the period 1975-1979 as the basis for this analysis. Because chemotherapy is not used for stage I disease, we assumed no improvement in survival of stage I disease over time. Improvements in survival for stage II, III and IV disease was a resultant of the hazard ratios of the introduction of newer chemotherapies compared to no chemotherapy and the dissemination of those therapies. For example in the latest time period, the following chemotherapies were available for treatment of stage IV disease: 5-fluouracil alone, 5-fluouracil + irinotecan, 5-fluouracil + oxaliplatin, and 5-fluouracil + biologics. The survival with each of these different treatments was calculated by applying the hazard ratios observed for these regimens compared to no chemotherapy that was observed in clinical trials to the survival hazards from 1975-1979 SEER-data (before the introduction of chemotherapy). The survival used for the latest time period was than equal to the average of the survival of the different chemotherapy regiments weighted by their dissemination in the population.

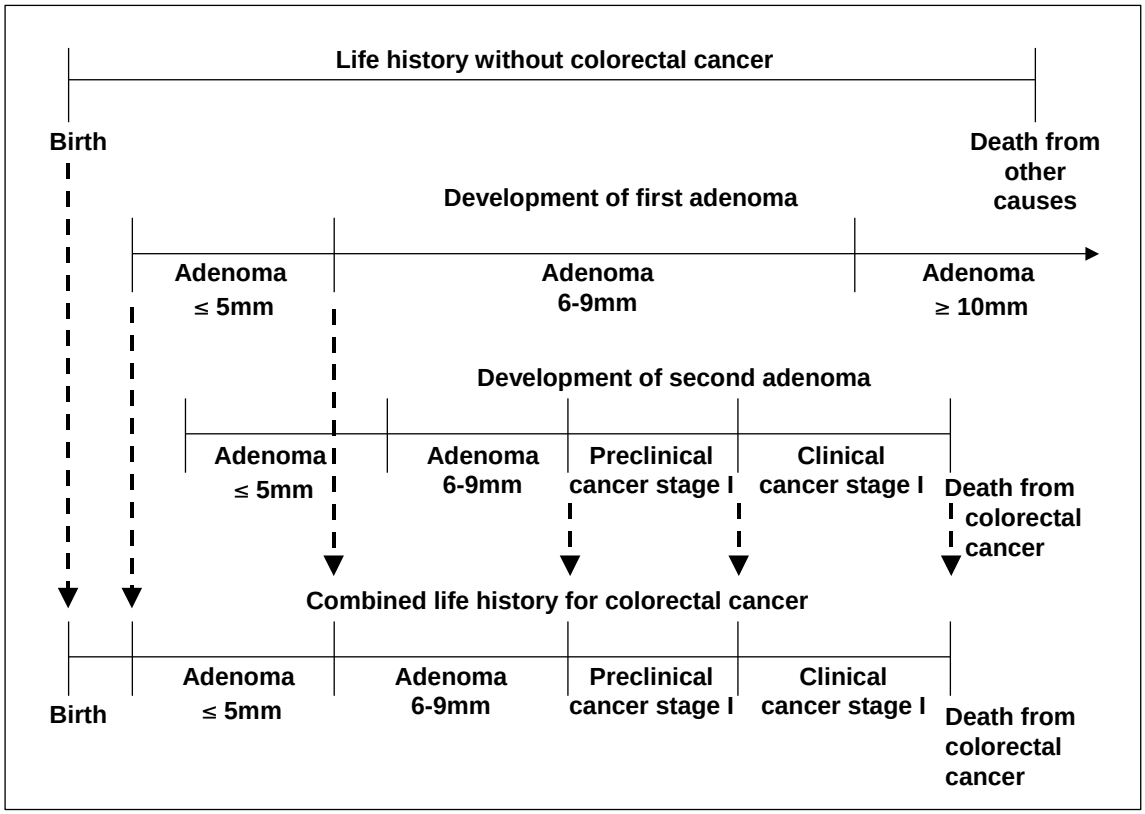
SCREENING PART

Screening interrupts the development of colorectal cancer. With screening, adenomas may be detected and removed and cancers may be found, usually in an earlier stage than with clinical diagnosis. We assumed the same stage-specific survival for screen-detected cases as for clinically diagnosed cases. In this way, screening prevents colorectal cancer incidence or colorectal cancer death. The life-years gained by screening are calculated by comparing the model-predicted life-years lived in the population with and without screening. The effects of different screening policies can be compared by applying them to identical natural histories.

INTEGRATION OF THE THREE MODEL COMPONENTS

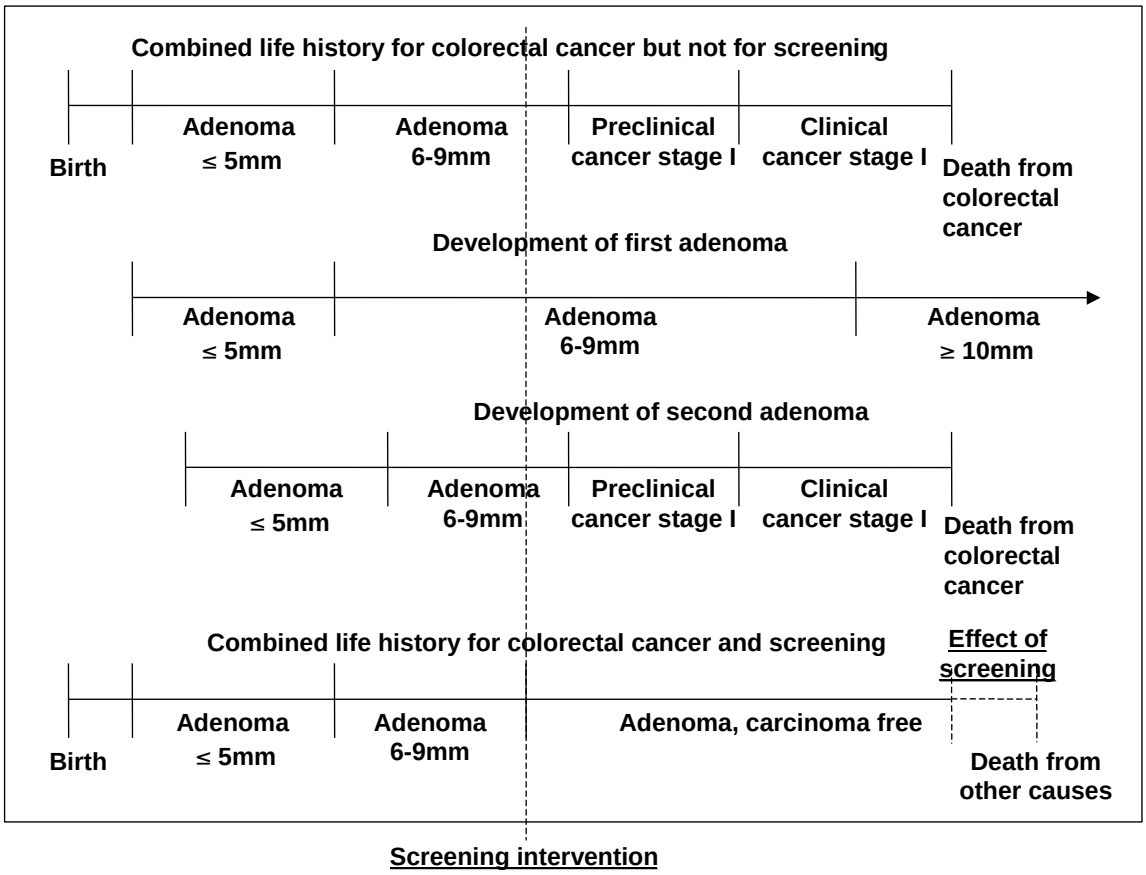
For each individual, the demography part of the model simulates a time of birth and a time of death from causes other than colorectal cancer, creating a life history without colorectal cancer (top line in Appendix Figure 3, A). Subsequently, adenomas are simulated for that individual. For most individuals, no adenomas are generated; for others, multiple adenomas are generated. In the example in Appendix Figure 3,A, the person develops two adenomas (2nd and 3rd line in Appendix Figure 3,A). The first adenoma arises at a certain age, grows to 6–9 mm, and eventually becomes larger than 10 mm. However, this adenoma does not become cancerous before the death of the person. The second adenoma is a progressive adenoma. After having grown to 6–9 mm, the adenoma transforms into a malignant carcinoma, causing symptoms followed by a colorectal cancer diagnosis and eventually resulting in an earlier death from colorectal cancer than death from other causes. The life history without colorectal cancer and the development of the two adenomas in Appendix Figure 3, A together lead to the combined life history with colorectal

cancer depicted in the bottom line. Because this person dies from colorectal cancer before he dies from other causes, his death age is adjusted accordingly.



Appendix Figure 3, A: Modeling natural history into life history

After the life history of a person is adjusted for colorectal cancer, the history is then adjusted for the effects of screening. The effect of screening on life history is explained in Appendix Figure 3, B. The top line in this figure is the combined life history for colorectal cancer from Appendix Figure 3, A. The development of the separate adenomas is repeated in the second and third line. In this figure, there is one screening intervention. During screening, both prevalent adenomas are detected and removed. Adding screening to the life history with colorectal cancer results in a combined life history for colorectal cancer and screening (bottom line). From the moment of screening, the adenomas are removed and this individual becomes adenoma- and carcinoma-free. This individual does not develop cancer because the precursor lesion has been removed. Therefore, the person no longer dies from colorectal cancer but from other causes and the effect of screening is equal to the difference in life-years between the situation without screening and the situation with screening. Of course, many other possibilities could have occurred: an individual could have developed new adenomas after the screening moment, or an adenoma could have been missed by the screening test, but in this case this individual really benefited from the screening intervention.



Appendix Figure 3, B: Modeling screening into life history

MODEL QUANTIFICATION

DEMOGRAPHY PARAMETERS

The MISCAN-Colon model is calibrated to reproduce the 1975-1979 age-specific CRC incidence rates by gender, representative of the US population prior to CRC screening. The life tables were derived from the 2000 US Life Table published by the National Center for Health Statistics (http://www.cdc.gov/nchs/products/pubs/pubd/lftbls/life/1966.htm). These life tables include colorectal cancer mortality, and the demography part simulates mortality from causes other than colorectal cancer.

NATURAL HISTORY PARAMETERS

The parameters for the natural history model for which no reference data were available were established based on expert opinion. At two meetings with experts in the field of colorectal cancer at the National Cancer Institute on June 5–7, 1996, and May 12–13, 1997, a model structure was devised in agreement with the currently accepted model of the adenoma–carcinoma sequence. It was assumed that all cancers are preceded by adenomas.

The expert panel agreed on an estimate of the average sojourn time (ie, the duration between the onset of a progressive adenoma and the clinical diagnosis of subsequent cancer) of 20 years. The average duration of cancer in preclinical stages I, II, III, and IV was 2 years, 1 year, 1.5 years, and 0.8 year, respectively, which resulted in a total average duration of 3.6 years because not every cancer reaches stage IV before clinical diagnosis. These sojourn times were based on the ratio of the stage-specific detection rate at first screening in fecal occult blood test trials to the background incidence, assuming a 60% sensitivity of fecal occult blood test for all cancer stages (4, 5). All durations were governed by an exponential probability distribution. Durations in each of the invasive cancer stages as well as durations in the stages of the noninvasive adenomas were assumed to be 100% associated with each other (e.g. if an adenoma grows very fast from small to medium size, it will also grow fast from medium to large). The durations in invasive stages as a whole were independent of durations in noninvasive adenoma stages that precede cancer. These assumptions resulted in an exponential distribution of the total duration of progressive noninvasive adenomas and of the total duration of preclinical cancer, which has also been used in other cancer screening models (4, 6).

It was assumed that 30% of the cancers arise from 6–9-mm adenomas and that 70% arise from larger adenomas. Initially, the preclinical incidence of progressive adenomas was chosen to reproduce the colorectal cancer incidence by age, stage, and localization in the United States in 1975–1979 (7). During this period, almost no screening was performed. The size distribution of adenomas over all ages was assumed to be 56% for adenomas less than or equal to 5 mm, 24% for adenomas 6–9 mm, and 20% for adenomas greater than or equal to 10 mm (8-17). The preclinical incidence of non-progressive adenomas that will never grow into cancer was varied until the simulated prevalence of all adenomas was in agreement with data from autopsy studies (8-17). The stage-specific survival after the clinical diagnosis of colorectal cancer is taken from the Surveillance, Epidemiology, and End Results registry data for 1990–1994 for the past scenario and for 1998–2003 for the present scenario (7). Appendix Table 1 contains a summary of the model input values and the data sources.

Appendix Table 1: Main natural history assumptions in the MISCAN-Colon model

Model parameter	Value	Source
Distribution of risk for adenomas over the general population	Gamma distributed, mean 1, variance 1.8	Fit to multiplicity distribution of adenomas in autopsy studies (8-17)
Adenoma incidence in general population	Race, sex, age and calendar time dependent.	Fit to adenoma prevalence in autopsy studies (8-17) and to cancer incidence in 1975–1979 in SEER registry (per 100,000) (7)
Probability that a new adenoma is progressive	Dependent on sex and age at onset:	Fit to adenoma prevalence in autopsy studies (8-17), cancer incidence in SEER registry in 1978 (7)
Regression of adenomas	No clinically significant regression of adenomas	Expert opinion
Mean duration of development of progressive adenomas to clinical cancer	20 years	Expert opinion*
Mean duration of preclinical cancer	3.6 years	Estimated from cancer detection rate at first screening and background cancer incidence in FOBT trials (4, 5)
Mean duration of adenoma	16.4 years	20 years minus 3.6 years
Percentage of non-progressive adenomas that stay 6–9 mm	50%	Fit to size distribution of adenomas in autopsy studies (8-17): 1–5 mm: 56% 6–9 mm: 24% ≥10 mm: 20%
Percentage of non-progressive adenomas that become 10 mm or larger	50%	Fit to size distribution of adenomas in autopsy studies (8-17): 1–5 mm: 56% 6–9 mm: 24% ≥10 mm: 20%
Percentage of cancers that develop from 6–9 mm adenoma and from ≥10-mm adenoma	30% of cancer develops from 6–9 mm, 70% from ≥10 mm	Expert opinion
Localization distribution of adenomas and cancer	Rectum: 31% Distal colon: 34% Proximal colon: 35%	Directly estimated from SEER 1997–2001 (7)

SEER: Surveillance, Epidemiology, and End Results; FOBT: Fecal Occult Blood Test;

* To be estimated from randomized controlled endoscopy trials, data not yet available.

RISK FACTOR PARAMETERS

The effects of the following eight modifiable risk factors known to be associated with colorectal cancer are included in the model:

- Smoking status* (yes/no)
- Obesity* (based on body mass index (BMI))
- Physical activity* (met-hours per week)
- Fruit and vegetable intake* (servings per day)
- Red meat intake (servings per day as a main dish)
- Aspirin/non-steroidal anti-inflammatory use (yes/no)
- Postmenopausal hormone replacement therapy (HRT) (yes/no)

Smoking, obesity and red meat consumption increase the chance of developing CRC, while physical activity, fruit and vegetable consumption, multivitamins, aspirin, and HRT have a preventive effect.

We used four waves of the National Health and Nutrition Examination Surveys (NHANES I, 1971-1975; NHANES II, 1976-1980; NHANES III, 1988-1994; 1999-2002) to estimate changes in CRC risk factors over time (18). We projected changes into the future for two sets of assumptions: 2005 Levels and Optimistic but Realistic. Appendix Table 2 shows the risk factor model inputs in 2005, 2010 and 2020 for each race/sex combination.

Appendix Table 2: Age-Adjusted Risk-Factor Prevalence in the MISCAN-COLON Microsimulation Model for 2005, 2010 and 2020*

Risk factor input	Race/gender group	2005 level	Optimistic but realistic	
			2010	2020
% current smokers	white male	21%	8%	4%
	white female	18%	8%	7%
	black male	29%	15%	10%
	black female	18%	8%	9%
% obese	white male	31%	30%	27%
	white female	38%	41%	45%
	black male	30%	29%	30%
	black female	56%	58%	57%
% moderate or vigorous physical activity	white male	33%	35%	42%
	white female	30%	33%	40%
	black male	37%	38%	38%
	black female	28%	32%	35%
% eating 5+ servings of fruits / vegetables per day	white male	44%	47%	51%
	white female	36%	39%	45%
	black male	37%	41%	48%
	black female	34%	37%	38%
% using multivitamins	white male	49%	62%	75%
	white female	48%	58%	68%
	black male	24%	30%	38%
	black female	30%	37%	36%
% receiving hormone replacement therapy	white female	10%	9%*	9%*
	black female	3%	3%*	3%*
% eating 2+ servings/week of red meat	white male	30%	29%	26%
	white female	23%	21%	16%
	black male	32%	32%	32%
	black female	24%	21%	17%
% Aspirin/NSAID users	white male	45%	50%*	56%*
	white female	46%	49%*	53%*
	black male	19%	19%*	19%*
	black female	24%	22%*	20%*

* Given the possible adverse effects of these risk factors, these risk factors were not considered as intervention options. For a complete overview of risk factor prevalence in the population, refer to: http://cisnet.cancer.gov/projections/colorectal/risk.php

We used the Nurses Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) to estimate the effect of risk factors on colorectal cancer incidence (19-33). The relative risks for adenomas and for CRC due to lifestyle risk factors are shown in Appendix Table 3. Values less than one signify a decrease in personal risk of CRC, while those over one signify increased risk. We assumed the effect of the risk factors to be multiplicative. Because the risk factors are assumed to only influence the onset of adenomas, there is a lag time of 10-20 years between the risk factor and the effect the risk factor has on colorectal cancer incidence. A longer lag time is for smoking is assumed (25-35 years).

Appendix Table 3: Risk Factors for Colorectal Carcinoma in the MISCAN-COLON Microsimulation Model: Categories of Exposure andAssumed Relative Risks for Developing Colorectal Adenomas

Risk factor for CRC	*Relative risk*
Smoking (smoker yes/no)	1.48
Obesity (BMI 30+)	1.33
Physical activity (20+ MET-hrs/week)	0.73
High vegetable consumption (5+ servings/day)	1.00
Red meat (2+ servings/week as a main dish)	1.33
Multivitamin use	0.63
Aspirin/NSAID use (~2+ tablets/week)	0.63
HRT use (post-menopausal women only)	0.73

SCREENING PARAMETERS

We incorporated the effects of the commonly-used screening tests of fecal occult blood test (FOBT) sigmoidoscopy and colonoscopy to assess their impact on colorectal cancer (CRC). NHIS provided rates for ever being screened and time since last screening by 5-year age groups in 1987, 1992, 1998, and 2000 (34). We assumed no screening prior to 1978. The screening rates between data points were estimated by linear extrapolation (see Table 2). Because of the poor performance characteristics of office-based FOBT (35), we accounted only for home-based FOBT. Because NHIS did not distinguish between home-based and office-based FOBTs before 2000, we estimated that the percentage of home-based FOBTs for earlier years would be the same as it was in 2000.

We used this information to determine the screening utilization for the two projection scenarios (2005 Levels and Optimistic but Realistic). Appendix Table 4 shows screening model inputs in 2005, 2010 and 2020 for each race/sex combination.

Appendix Table 4: Age-Adjusted Screening Dissemination in the MISCAN-COLON Microsimulation Model for 2005, 2010 and 2020*

Screening Input	Race/Sex Group	2005 Level	Optimistic but Realistic	
			2010	2020
% over age 50 have FOBT within past 2 years	white male	24%	22%	23%
	white female	25%	23%	25%
	black male	20%	22%	23%
	black female	23%	24%	26%
% over age 50 have had a sigmoidoscopy or colonoscopy at some point in their life *	white male	54%	63%	70%
	white female	49%	59%	69%
	black male	44%	50%	59%
	black female	43%	55%	64%

* For a complete overview of screening dissemination in the population, refer to: http://cisnet.cancer.gov/projections/colorectal/screening.php

Screen test characteristics for each test were based on existing literature (4, 36) (Appendix Table 5). Sensitivity is the likelihood that a test will find cancers or adenomas if they exist. Specificity is the probability of a negative result in patients free from any lesions. We assumed distinct sensitivities for small (1-5 mm), medium (6-9 mm) and large (10+ mm) adenomas as well as preclinical cancer.

Appendix Table 5: Characteristics of Home-Based Fecal Occult Blood Testing, Sigmoidoscopy, and Colonoscopy in the MISCAN-COLON Microsimulation Model: Sensitivity for Small, Medium, and Large Adenomas and Cancers; Specificity; and Reach

Test characteristic	Model assumption
FOBT	
Sensitivity for small, medium, large adenomas	2,2,5% (per adenoma)
Cancer sensitivity	60%
Specificity	98%
Reach	Whole colon and rectum
Compliance with follow-up	80%
Sigmoidoscopy	
Sensitivity for small, medium, large adenomas (within reach)	75,85,95%
Cancer sensitivity (within reach)	95%
Specificity	100%
Reach	75% reach descending colon, none beyond splenic flexure
Compliance with follow-up	80%
Colonoscopy	
Sensitivity for small, medium, large adenomas (within reach)	80,85,95%
Cancer sensitivity (within reach)	95%
Specificity	100%
Reach	95% reach ascending colon, 70% reach cecum

The stage-specific survival of patients with screen-detected cancer is assumed to be the same as the survival of patients with cancers clinically diagnosed in the same stage (37). Removal of an adenoma always prevents development of any subsequent cancer that may have arisen from this adenoma. Risks of complications reported in organized screening programs (38-40) are lower than those reported for general practice colonoscopies (41, 42). The major complications of colonoscopy are perforations (which can occur with or without polypectomy), serosal burns,

bleeds requiring transfusion, and bleeds not requiring transfusion (38-42). We estimated a rate of death of 0.1 per 1000 colonoscopies (43).

CHEMOTHERAPY PARAMETERS

There are four "eras" in CRC chemotherapy, based on the number of drugs approved and available for use with patients (Appendix Table 6). This is not to imply that in the later periods, all the available drugs are used in one regimen.

Appendix Table 6: Four "eras" in CRC chemotherapy, based on the number of drugs approved and available for use with patients

Era	Description	Available starting in:
1-drug	5-fluorouracil (5FU)	prior to 1996
2-drug	irinotecan (brand name: Camptosar)	1996
3-drug	oxaliplatin (brand name: Eloxatin®)	2002
4-drug	antibodies cetuximab or bevacizumab	2004

Effectiveness is measured by a hazard ratio which compares the death rate for patients receiving a given chemotherapy to the death rate for those receiving no chemotherapy (Appendix Table 7). A hazard ratio of 1.0 indicates no benefit from chemotherapy; ratios less than one mean extended survival due to the regimen, with lower numbers indicating greater effectiveness. Hazard ratios depend on stage at diagnosis and age. We derived hazard ratios on the basis of review of all phase III clinical trials of chemotherapy for colon and rectal cancers published in English since 1970 (44-54).

Appendix Table 7 shows the hazard ratios used to compute risk of death from CRC, given various chemotherapy regimens. Note that effectiveness decreases for those 75 years of age and older, although chemotherapy still offers significant benefit. Note also that we use the same hazard ratio for stage II and III cancer. Although clinical trials for stage II disease have shown a trend towards benefit of chemotherapy, they have not been statistically significant. This may be an artifact of the highly favorable prognosis for stage II patients; it would take a very large number of patients to demonstrate a statistically significant improvement. Many stage II patients do get treatment, and all of the trials have had a trend in favor of treatment that just has not reached significance.

Appendix Table 7: Hazard Ratios of Dying from Colorectal Carcinoma for Various Chemotherapy Treatment Regimens Compared with no Adjuvant Chemotherapy in the MISCAN-COLON Microsimulation Model

Chemotherapy	Stage II or III		Stage IV	
	< 75 years	75+ years	< 75 years	75+ years
No chemotherapy	1.00	1.00	1.00	1.00
5FU	0.74	0.82	0.70	0.80
5FU + irinotecan			0.60	0.70
FOLFOX*	0.61	0.71	0.50	0.60
FOLFOX + antibodies			0.42	0.46

*Chemotherapy regimen consisting of concurrent treatment with 5-fluorouracil, leucovorin, and oxaliplatin.

Dissemination of chemotherapy is based on analyses of the SEER-Medicare linked dataset (55, 56), extrapolated for patients aged less than 65 years at diagnosis based on Patterns-of-Care studies (57, 58). Our modeling for the future is based on projections of patterns of use. Appendix Table 8 shows chemotherapy model inputs in 2005, 2010 and 2020 for each race/sex combination.

Appendix Table 8: Age-Adjusted Treatment Use for Colorectal Cancer in the MISCAN-COLON Microsimulation Model for 2005, 2010 and 2020*

Chemotherapy Input	Race/Sex Group	2005 Level	Optimistic but Realistic	
			2010	2020
-- for stage II cancer				
% not receiving chemotherapy	white male + female	51%	47%	47%
	black male + female	59%	47%	47%
% receiving 5FU	white male + female	20%	0%	0%
	black male + female	16%	0%	0%
% receiving FOLFOX	white male + female	29%	53%	53%
	black male + female	25%	53%	53%
-- for stage III cancer				
% not receiving chemotherapy	white male + female	24%	19%	19%
	black male + female	36%	19%	19%
% receiving 5FU	white male + female	28%	0%	0%
	black male + female	23%	0%	0%
% receiving FOLFOX	white male + female	48%	81%	81%
	black male + female	41%	81%	81%
-- for stage IV cancer				
% not receiving chemotherapy	white male + female	30%	23%	23%
	black male + female	41%	23%	23%
% receiving 5FU	white male + female	5%	0%	0%
	black male + female	4%	0%	0%
% receiving 5FU + irinotecan	white male + female	1%	0%	0%
	black male + female	1%	0%	0%
% receiving FOLFOX	white male + female	13%	0%	0%
	black male + female	11%	0%	0%
% receiving FOLFOX + antibodies	white male + female	50%	77%	77%
	black male + female	43%	77%	77%

* For a complete overview of assumed chemotherapy use in the population, refer to: http://cisnet.cancer.gov/projections/colorectal/chemo.php

MODEL OUTPUTS

The model generates the following output, both undiscounted and discounted:

Demography

1. Life-years lived in the population by calendar year, age, and gender
2. Deaths from other causes than colorectal cancer by calendar year, age, and gender

Natural history

1. Colorectal cancer cases by calendar year, stage, age, and gender
2. Colorectal cancer deaths by calendar year, age, and gender
3. Life-years lived with colorectal cancer by calendar year, stage, age, and gender
4. Total number of life years with surveillance for adenoma patients
5. Total number of life years with initial therapy after screen-detected or clinical invasive cancer by stage
6. Total number of life years with continuing therapy after screen-detected or clinical invasive cancer by stage
7. Total number of life years with terminal care before death from other causes by stage
8. Total number of life years with terminal care before death from colorectal cancer by stage

Screening

1. Number of screening invitations, screen-tests, diagnostic tests, surveillance, and opportunistic screen tests by calendar year
2. Number of positive and negative test results per preclinical state and per year
3. Total number of life years lived, life years lost due to cancer, number of specific deaths and non-specific deaths
4. Number of screenings that prevented cancer by year of screening
5. Number of screenings that detected cancer early by year of screening
6. Number of surveillance tests that prevented cancer by year of surveillance
7. Number of surveillance tests that detected cancer early by year of surveillance
8. Number of life years gained due to screening by year of screening

PRODUCTIVITY COST ESTIMATION

Overview

We used the human capital method with an incidence-based approach to estimate the costs of cancer deaths that occurred and are predicted to occur between 2000 and 2020. The base model reflects employment and income transitions over the lifecycle by summing the expected earnings in each year of forgone life over a given life expectancy, accounting for changes in the probability of employment and wages that occur from year to year and from age group to age group. For example, life expectancy for a managed 35 in 2000 was an additional 42.2 years. Using assumptions in our model, a man who died at age 35 years in 2000 had a 0.93 probability of being employed, and his average annual full-time earnings plus the value of fringe benefits would be $56,519. Had he lived, his probability of employment would have decreased to 0.87 at age 50, but his annual average earnings would have increased to $87,706 (including fringe benefits) in the year 2015. His probability of employment would have further decreased at age 65 in the year 2030 and continued to decline for his remaining life span. The model accounts for such year-by-year transitions in employment probabilities and expected earnings throughout the expected lifetime of the individuals who would have otherwise lived in the absence of cancer.

We report the present value of lifetime earnings (PVLE) as the sum of productivity costs and the sum of the imputed value of caregiving and household activities. Thus, the PVLE takes into account life expectancy for different sex and age groups, the percentage of people in the labor force and/or those who are engaged in caregiving and household activities, the current pattern of earnings at successive ages, an imputed value of caregiving and household activities, and the discount rate. A discount rate (3%) is applied to convert future dollars to their present value.

Model Inputs

The base model used aggregate age- and sex-specific data from four sources. First, the US Bureau of the Census provided the National Interim Projections of the US population from 2000 through 2020 (59). Second, US death certificate data covering 1999 through 2003 was used to estimate age-adjusted cancer site-specific mortality rates. Third, cohort life tables from the Berkeley Mortality Database for birth years 1900–2000 were used to estimate and project sex-specific life expectancy in the years 2000–2020. The Berkeley Mortality Database, which was developed from historical series of national vital statistics (ie, births, deaths, and census populations), is part of the Human Mortality Database project, whose aim is to construct high-quality national cohort life tables. Projections incorporate observed trends in life expectancy in the past century. Because these life tables only contain years of birth through 2000, we assumed that individuals born after 2000 (ie, 2001–2020) would have the same life expectancy as those born in 2000. These cohort life table data and related documentation are available at http://www.demog.berkeley.edu/~bmd/states.html (60).

Employment and Wages

All estimates of wages, employment rates, and full- and part-time employment rates were from the Current Population Survey (CPS). The CPS is a monthly survey of households that is conducted by the Bureau of the Census for the Bureau of Labor Statistics (BLS); it is the primary source of information on labor force characteristics and behavior of the US population (61).

Fringe benefits constitute approximately 27.4% of compensation (62). These benefits include vacation pay, health insurance, retirement benefits, and annual and personal leave. It has been argued (62) that paid leave should not be used to adjust annual earnings. Therefore, Grosse (62) suggests that annual earnings should be adjusted upward by 22.4% instead off 27.4% to reflect the absence of paid leave and to compensate for worker categories (eg, agricultural workers) that do not have generous benefits (62). Following the example set by Grosse, we used a rate of 22.4% to upwardly adjust annual earnings for full-time workers and a rate of 10.3% to upwardly adjust part-time workers' annual earnings.

Caregivers and Housekeepers

Two additional data sources were used to estimate the number of caregivers and housekeepers in the populations. First, we use estimates from Grosse (62) of the number of individuals who were engaged in both housekeeping and caregiving. These estimates are based on responses to the National Human Activity Pattern Survey (NHAPS) administered by the U.S. Environmental Protection Agency. This survey collected information on household production (housework, food cooking and clean-up, taking care of plants and animals, home and auto maintenance, and obtaining goods and services) and providing care (childcare, child guidance, playing with children, transporting children, helping and caring for adults, helping adults with other personal activities, and personal care travel). Grosse (12) used these estimates to determine the prevalence of individuals living in households and time spent on various caregiving and household activities and then applied a wage rate, derived from the CPS, corresponding to the proportion of time spent doing various activities. Imputed housekeeping and caregiving wages were then adjusted up by a fringe benefit rate ranging from 10.3% to 14.1% (12). The second source was the *Caregiving in the U.S.* study (63), which was conducted by the National Alliance for Caregiving and the American Association of Retired Persons (AARP). This national survey identified 1247 caregivers primarily through the random digit dial technique and collected precise information on hours spent caregiving and the type of care provided. The estimates for caregiving and household activities reflect the value of unpaid activities in which individuals would have been engaged if they had not died from cancer. We used this study to estimate the percentage of the US population who were engaged in caregiving and, among those individuals, the percentage who provided round-the-clock care.

Estimation

The model used mean weekly wages by sex for all races and occupations combined for the years 2000–2006, available from the BLS upon request. Wages were reported for the 5-year age groups of interest but were combined for all ages 70 years and older. The model used the wages published in Grosse (62) to determine the imputed value of caregiving and household activities. Different wage rates were imputed for caregivers and housekeepers; these wages were then weighted by the time spent engaged in each type of activity. For example, a typical single individual without children who is employed full-time spends less time engaged in caregiving and household activities than an unemployed individual with children.

To estimate wages for future years, wages were adjusted beyond 2006 for inflation using the Consumer Price Index (CPI) (64). Annual Inflation conversion factors were 2.1% in 2007 and 2.2% in 2008–2020. The CPI-inflated wages were used as a proxy for real future wages.

The model then incorporated estimates of full- and part-time employment from the BLS for the years 2000 through 2007 for individuals who were age 18–79 years. Because comparable estimates were not available for individuals who were age 80 years and older, we applied the rates for the 75–79 year age group to those who were age 80 and older. We used the average employment rates from 2000 through 2007 to project future employment rates.

According to the *Caregiving in the U.S.* survey, approximately 21% of the US population older than 18 years is engaged in caregiving activities, which includes housekeeping chores. Approximately 10% of these caregivers provide more than 40 hours per week of care and assist another individual with two or more Activities of Daily Living (ADLs). Therefore, we assigned an annual earnings equivalent as the annual charge for nursing home care, which was $74,000 in 2005, and adjusted it using the CPI and a projection of the CPI for future years (65). This level of care was projected to last for 2.4 years, the average length of time patients reside in a nursing home (66).

Because a 20-year-old individual in 2020 was expected to live 62 additional years, all estimates of wages, employment, and caregiver and housekeeping rates were projected to 2082 to account for the maximum number of years this cohort of individuals could have lived. The number of deaths, PYLL, employment and caregiver and housekeeper rates, wages by sex and age, and the average PVLE for the year 2000 are reported (See Appendix Table 9).

Appendix Table 9: Model inputs and average present value of lifetime earnings (PVLE) for the year 2000*

Sex and age, y	No. of deaths	Mean person-years of life lost	Person years of life lost	Percent employed	Percent employed full-time	Percent employed part-time	Annual mean full-time earnings, $US	Annual mean part-time earnings, $US	Mean PVLE, $US	Proportion of persons living in households	Adjusted caregiving & household wages, $US	Mean PVLE including caregiving & household wages in $US
Females												
20–24	394	61.39	24,190	73.3	69.0	31.0	27,050	12,188	1,338,188	91.5	9806	2,230,023
25–29	657	56.12	36,870	77.1	82.0	18.0	39,271	17,694	1,284,081	99.2	13,233	2,142,912
30–34	1378	51.07	70,370	75.6	82.0	18.0	41,308	18,612	1,167,549	99.2	13,233	1,972,799
35–39	3148	45.94	144,600	75.8	80.0	20.0	43,917	19,788	1,019,631	99.5	15,000	1,767,713
40–44	5956	40.93	243,760	78.7	80.0	20.0	43,917	19,788	873,166	99.5	15,000	1,551,323
45–49	9442	35.98	339,710	77.0	82.0	18.0	45,954	20,706	704,211	99.3	14,958	1,309,721
50–54	14,010	31.18	436,830	74.1	82.0	18.0	48,182	21,709	519,640	99.3	14,958	1,050,032
55–59	17,675	26.57	469,680	59.7	75.0	25.0	45,572	20,533	335,524	99.3	16,334	791,482
60–64	22,199	22.27	494,290	39.1	75.0	25.0	43,217	19,472	179,874	99.3	16,334	555,047
65–69	28,540	18.29	522,110	18.8	41.0	59.0	34,115	15,371	72,285	98.1	15,871	363,558
70–74	37,440	14.67	549,330	9.7	41.0	59.0	32,651	14,712	33,291	98.1	15,871	240,800
75–79	42,004	11.37	477,460	3.5	41.0	59.0	32,651	14,712	16,821	87.3	13,606	174,422
80–84	36,395	8.48	308,500	3.5	41.0	59.0	32,651	14,712	11,531	87.3	13,606	114,175
≥85	42,777	5.30	226,850	3.5	41.0	59.0	32,651	14,712	6144	87.3	13,606	81,229
Males												
20–24	553	56.09	31,020	82.6	81.0	19.0	28,960	13,048	2,158,521	87.9	5234	2,692,877
25–29	699	51.03	35,670	92.4	95.0	5.0	43,090	19,415	2,100,893	96.4	7396	2,623,380
30–34	1164	46.16	53,730	94.2	95.0	5.0	49,200	22,168	1,944,784	96.4	7396	2,440,182
35–39	2325	41.25	95,890	93.2	97.0	3.0	56,519	25,466	1,721,472	97.8	9210	2,187,183
40–44	4869	36.46	177,520	92.1	97.0	3.0	58,747	26,470	1,464,748	97.8	9210	1,893,059
45–49	9153	31.72	290,310	90.1	96.0	4.0	60,593	27,301	1,195,154	98.7	9229	1,579,902
50–54	14,989	27.09	406,120	86.8	96.0	4.0	62,821	28,305	906,994	98.7	9229	1,250,273
55–59	20,535	22.68	465,640	77.1	90.0	10.0	59,638	26,871	623,565	98.7	11,234	921,947
60–64	27,265	18.59	506,710	54.8	90.0	10.0	54,928	24,749	340,503	98.7	11,234	584,905
65-69	35,826	14.94	535,180	30.1	55.0	45.0	46,272	20,849	167,294	98.2	12,395	377,325
70–74	45,706	11.74	536,690	17.9	55.0	45.0	48,245	21,738	79,668	98.2	12,395	229,796
75–79	47,732	8.93	426,230	8.0	55.0	45.0	48,245	21,738	41,351	93.1	11,351	138,485
80–84	36,849	6.63	244,260	8.0	55.0	45.0	48,245	21,738	27,890	93.1	11,351	103,292
≥85	31,997	4.42	141,260	8.0	55.0	45.0	48,245	21,738	17,832	93.1	11,351	58,479

*PVLE=Present value of lifetime earnings. Annual earnings are adjusted up by 22.4% to include the value of fringe benefits. Part-time earnings are adjusted by 10.3% to include fringe benefits. Persons living in households and the upwardly adjusted caregiving and household wages are from Grosse (62). We assume that 2.1% of the population provides care for an individual that would otherwise be institutionalized. For these individuals, this care is provided for 2.4 years, which is the average nursing home length of stay, and estimated at a value of $74,000 per year. Estimates of persons living in households and their adjusted wages are from Gross (62).

Morbidity costs

The National Health Interview Survey (NHIS) collects data on respondents' inability to work due to health limitations and work loss days. CRC attributable to non-employment (ΔNE_{CRC}) was calculated as the difference between the percentage of NHIS respondents with CRC and those without cancer by age and gender who report they cannot work due to a disability. Similarly, the difference in percent of work hours lost due to a health condition is estimated between those with and without CRC (ΔH_{CRC}) (see Appendix Table 10).The cost of productivity loss due to morbidity is estimated using employment rates, wage estimates, and a discount rate as described in the proceeding section as Productivity x S_{CRC} x $\left(\Delta NE_{CRC} + \Delta H_{CRC} g E_{CRC}\right)$, where E_{CRC} and S_{CRC} are the rates of employment and number of CRC survivors. The MISCAN's intervention-specific projections of incidence and mortality reductions are applied to the cost of CRC mortality and morbidity productivity losses by gender and 5-year age group.

Appendix Table 10. NHIS Work rates, disability rates, and work loss days by CRC survivors and non-cancer respondents

		% Job in past 12 months		% Unable to work because of health		% Limited in amount/kind of work because of health		Mean work loss days past 12 months	
Males	Age group	*CRC Survivors (N=838)	Non-cancer Respondents (N=138,687)	CRC Survivors (N=843)	Non-cancer Respondents (N=139,368)	CRC Survivors (N=841)	Non-cancer Respondents (N=139,098)	CRC Survivors (N=236)	Non-cancer Respondents (N=108,414)
	<45	66.2	92.3	36.1	2.9	39.4	5.2	8.6	3.4
	45-49	81.6	92.0	23.5	6.3	27.2	9.8	5.9	5.0
	50-54	75.8	89.0	31.7	8.3	36.8	12.6	41.1	4.5
	55-59	62.4	81.1	26.6	11.2	40.1	16.2	11.4	4.6
	60-64	55.0	62.8	21.3	13.9	29.7	19.9	11.2	4.8
	65-69	30.0	37.8	15.3	10.5	29.2	19.1	12.3	4.1
	70-74	20.9	22.9	15.3	9.8	26.9	19.3	5.2	3.6
	75-79	12.0	14.6	15.4	12.0	31.0	23.4	1.7	4.4
	80+	6.2	7.4	25.1	17.7	35.7	31.3	4.3	3.3
	All ages	31.0	81.3	20.9	6.0	32.3	10.0	12.3	3.9
Females	Age group	*CRC Survivors (N=1,011)	Non-cancer Respondents (N=175,572)	CRC Survivors (N=1,021)	Non-cancer Respondents (N=176,867)	CRC Survivors (N=1,020)	Non-cancer Respondents (N=176,468)	CRC Survivors (N=211)	Non-cancer Respondents (N=111,600)
	<45	48.3	79.7	21.9	3.1	37.5	5.4	53.7	4.2
	45-49	56.2	81.5	47.0	6.7	52.6	10.5	24.8	4.8
	50-54	69.5	77.6	39.9	8.7	53.9	13.5	50.3	5.4
	55-59	64.8	68.7	20.5	11.4	23.6	17.1	4.3	5.1
	60-64	45.4	49.5	14.4	12.6	23.1	19.3	3.8	5.0
	65-69	27.5	27.1	20.0	10.5	32.4	18.6	1.3	4.5
	70-74	7.4	14.2	19.6	11.2	30.7	21.2	3.1	3.5
	75-79	8.1	7.8	21.8	13.6	32.7	24.6	7.8	2.8
	80+	3.2	2.9	19.2	21.3	33.4	34.3	11.4	1.3
	All ages	22.0	66.7	21.5	6.8	33.1	11.2	17.9	4.4

References

1. Morson B. President's address. The polyp-cancer sequence in the large bowel. Proc R Soc Med 1974;67(6):451-7.
2. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med 1988;319(9):525-32.
3. Sobin L, Wittekind C, editor. TNM classification of malignant tumours. 6th edition ed. New York: Wiley-Liss; 2002.
4. Gyrd-Hansen D, Sogaard J, Kronborg O. Analysis of screening data: colorectal cancer. Int J Epidemiol 1997;26(6):1172-81.
5. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348(9040):1472-7.
6. Launoy G, Smith TC, Duffy SW, Bouvier V. Colorectal cancer mass-screening: estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. Int J Cancer 1997;73(2):220-4.
7. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 9 Regs Limited-Use, Nov 2002 Sub (1973-2000). In: National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2003, based on the November 2002 submission; 2003.
8. Arminski TC, McLean DW. Incidence and Distribution of Adenomatous Polyps of the Colon and Rectum Based on 1,000 Autopsy Examinations. Dis Colon Rectum 1964;7:249-61.
9. Blatt L. Polyps of the Colon and Rectum: Incidence and Distribution. Dis Colon Rectum 1961;4:277-282.
10. Bombi JA. Polyps of the colon in Barcelona, Spain. An autopsy study. Cancer 1988;61(7):1472-6.
11. Chapman I. Adenomatous polypi of large intestine: incidence and distribution. Ann Surg 1963;157:223-6.
12. Clark JC, Collan Y, Eide TJ, Esteve J, Ewen S, Gibbs NM, et al. Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. Int J Cancer 1985;36(2):179-86.
13. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. Gut 1992;33(11):1508-14.
14. Johannsen LG, Momsen O, Jacobsen NO. Polyps of the large intestine in Aarhus, Denmark. An autopsy study. Scand J Gastroenterol 1989;24(7):799-806.
15. Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel: an autopsy survey. Cancer 1979;43(5):1847-57.
16. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. Cancer 1982;49(4):819-25.
17. Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982;23(10):835-42.
18. National Health and Nutrition Examination Survey. In: Centers for Disease Control and Prevention, National Center for Health Statistics.
19. Giovannucci E, Colditz GA, Stampfer MJ, Hunter D, Rosner BA, Willett WC, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. J Natl Cancer Inst 1994;86(3):192-9.
20. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Kearney J, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. J Natl Cancer Inst 1994;86(3):183-91.
21. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med 1995;122(5):327-34.

22. Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk of colorectal adenoma in women (United States). Cancer Causes Control 1996;7(2):253-63.
23. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. Comparison of risk factors for colon and rectal cancer. Int J Cancer 2004;108(3):433-42.
24. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54(9):2390-7.
25. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, et al. Aspirin and the risk of colorectal cancer in women. N Engl J Med 1995;333(10):609-14.
26. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. Ann Intern Med 1994;121(4):241-6.
27. Chan AT, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, et al. A prospective study of aspirin use and the risk for colorectal adenoma. Ann Intern Med 2004;140(3):157-66.
28. Giovannucci E, Stampfer MJ, Colditz GA, Hunter DJ, Fuchs C, Rosner BA, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. Ann Intern Med 1998;129(7):517-24.
29. Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993;85(11):875-84.
30. Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC. Relationship of diet to risk of colorectal adenoma in men. J Natl Cancer Inst 1992;84(2):91-8.
31. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Stampfer MJ, Rosner B, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. N Engl J Med 1999;340(3):169-76.
32. Michels KB, Edward G, Joshipura KJ, Rosner BA, Stampfer MJ, Fuchs CS, et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. J Natl Cancer Inst 2000;92(21):1740-52.
33. Grodstein F, Martinez ME, Platz EA, Giovannucci E, Colditz GA, Kautzky M, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. Ann Intern Med 1998;128(9):705-12.
34. National Health Interview Survey. In: Centers for Disease Control and Prevention, National Center for Health Statistics.
35. Collins JF, Lieberman DA, Durbin TE, Weiss DG. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. Ann Intern Med 2005;142(2):81-5.
36. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101(2):343-50.
37. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348(9040):1467-71.
38. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. N Engl J Med 2000;343(3):162-8.
39. Pox C, Schmiegel W, Classen M. Current status of screening colonoscopy in Europe and in the United States. Endoscopy 2007;39(2):168-73.
40. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355(18):1863-72.
41. Levin TR, Conell C, Shapiro JA, Chazan SG, Nadel MR, Selby JV. Complications of screening flexible sigmoidoscopy. Gastroenterology 2002;123(6):1786-92.
42. Levin TR, Zhao W, Conell C, Seeff LC, Manninen DL, Shapiro JA, et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 2006;145(12):880-6.
43. Jentschura D, Raute M, Winter J, Henkel T, Kraus M, Manegold BC. Complications in endoscopy of the lower gastrointestinal tract. Therapy and prognosis. Surg Endosc 1994;8(6):672-6.

44. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 1995;345(8955):939-44.
45. Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer. International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators. J Clin Oncol 1999;17(5):1356-63.
46. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351(4):337-45.
47. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18(16):2938-47.
48. Gill S, Loprinzi CL, Sargent DJ, Thome SD, Alberts SR, Haller DG, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22(10):1797-806.
49. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22(1):23-30.
50. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350(23):2335-42.
51. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, et al. Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes' B2 colon cancer. J Clin Oncol 1995;13(12):2936-43.
52. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Tangen CM, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995;122(5):321-6.
53. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 2000;343(13):905-14.
54. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22(2):229-37.
55. Warren JL, Harlan LC, Fahey A, Virnig BA, Freeman JL, Klabunde CN, et al. Utility of the SEER-Medicare data to identify chemotherapy use. Med Care 2002;40(8 Suppl):IV-55-61.
56. Schrag D, Rifas-Shiman S, Saltz L, Bach PB, Begg CB. Adjuvant chemotherapy use for Medicare beneficiaries with stage II colon cancer. J Clin Oncol 2002;20(19):3999-4005.
57. Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF. Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. J Clin Oncol 2002;20(5):1192-202.
58. Ayanian JZ, Zaslavsky AM, Fuchs CS, Guadagnoli E, Creech CM, Cress RD, et al. Use of adjuvant chemotherapy and radiation therapy for colorectal cancer in a population-based cohort. J Clin Oncol 2003;21(7):1293-300.
59. U.S. Bureau of the Census. National Interim Projections. http://www.census.gov/ipc/www/usinterimproj/ . Accessed June 2007.
60. Berkeley Mortality Database. http://www.demog.berkeley.edu/~bmd/states.html. Accessed June 2005.
61. U.S. Department of Labor, Bureau of Statistics and U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. Current Population Survey, Design and Methodology, Technical Paper TP63RV, Washington, D.C. http://www.bls.census.gov/cps/tp/tp63.htm. Accessed August 2007.

62. Grosse S. Appendix I: Productivity Loss Tables in Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation. 2nd Edition. Eds Haddix A, Teutsch S, and Corso P. Oxford University Press. 2003.
63. National Alliance for Caregiving and the American Association of Retired Persons, Caregiving in the U.S. 2004.
64. U.S. Department of Labor, Bureau of Statistics, Consumer Price Index. http://stats.bls.gov/cpi/home.htm#data. Accessed December 2006.
65. Metlife Market Survey of Nursing Home and Home Care Costs, 2005, http://www.metlife.com/WPSAssets/41453139101127828650V1F2005%20NH%20and%20HC%20Market%20Survey.pdf. Accessed May 2007.
66. National Center for Health Statistics. National Nursing Home Survey. Centers for Disease Control. Atlanta, GA. http://www.cdc.gov/nchs/about/major/nnhsd/ResidentTables_Estimates.htm#PaymentSource. Accessed June 2008.